Qualitative and Quantitative Assessment of Stent Restenosis by Optical Coherence Tomography
– Comparison Between Drug-Eluting and Bare-Metal Stents –

Ryoji Nagoshi, MD; Toshiro Shinke, MD; Hiromasa Otake, MD; Junya Shite, MD; Daisuke Matsumoto, MD; Hiroyuki Kawamori, MD; Masayuki Nakagawa, MD; Amane Kozuki, MD; Hirotoshi Hariki, MD; Takumi Inoue, MD; Tsuyoshi Ohsue, MD; Yu Taniguchi, MD; Masamichi Iwasaki, MD; Ryo Nishio, MD; Noritoshi Hiranuma, MD; Akihide Konishi, MD; Hiroto Kinutani, MD; Naoki Miyoshi, MD; Tomofumi Takaya, MD; Shinichiro Yamada, MD; Yoshinori Yasaka, MD; Takatoshi Hayashi, MD; Mitsuhiro Yokoyama, MD; Hiroki Kato, MD; Makoto Kadotani, MD; Yoshio Ohnishi, MD; Ken-ichi Hirata, MD

Background: We hypothesized that the tissue components of in-stent restenosis (ISR) might differ between drug-eluting stents (DES) and bare-metal stents (BMS) and that these differences could be distinguished by qualitative and quantitative optical coherence tomography (OCT) analyses.

Methods and Results: One-hundred and twenty-two initial ISR lesions (sirolimus-eluting stents: n=28; paclitaxel-eluting stents: n=51; BMS: n=43) were evaluated with OCT. Based on their OCT appearance, the lesions were classified as homogeneous, layered or heterogeneous. The optical properties of backscatter, attenuation and signal intensity of the neointimal tissue (NIT) were quantified. To evaluate the vascular response after balloon angioplasty (BA), the rate of reduction of the NIT area (NITA) was calculated (NITA before – after BA/NITA before at the minimum lumen cross-sectional area). Among the morphologic OCT patterns, the layered type was predominant with DES, whereas lesions were homogeneous with BMS (P<0.001). Backscatter and signal intensity were significantly higher with BMS (P<0.05 and P<0.001 respectively). The NITA reduction rate was significantly greater in the layered and heterogeneous groups than in the homogeneous group (P<0.01).

Conclusions: The morphologic OCT patterns of the NIT in ISR differed significantly between DES and BMS, probably reflecting pathologic differences. Layered and heterogeneous tissues might respond better than homogeneous tissue to simple balloon dilatation, suggesting a possible direction for OCT-based ISR treatment strategies. (Circ J 2013; 77: 652 – 660)

Key Words: Bare-metal stents; Drug-eluting stents; In-stent restenosis; Optical coherence tomography

B ased on several pathologic studies performed after stenting, neointimal tissue (NIT) has various components, including proteoglycans, organized thrombi, smooth muscle cells, atheromas, inflammatory cells, and fibrinoids.1-6 Whether these tissue components differ between the in-stent restenosis (ISR) lesions of drug-eluting stents (DES) and bare-metal stents (BMS) is controversial. Van Beusekom et al reported a higher incidence of fibrinoid deposits in ISR lesions following DES implantation than following BMS implantation based on a pathologic analysis of 25 human ISR specimens obtained by atherectomy,7 but Chieffo et al reported that tissue components were similar between DES and BMS ISR lesions.8 Angiographic and intravascular ultrasound (IVUS) assessments of ISR lesions are limited to visualization of the
We enrolled a total of 99 patients with 122 ISR lesions with DES (79 lesions in 61 patients; SES: 28 lesions in 25 patients, PES: 51 lesions in 36 patients) and BMS (43 lesions in 38 patients). All of the index stent placements were performed with IVUS guidance (Boston Scientific or Volcano Corporation, Rancho Cordova, CA, USA). All patients had been taking aspirin (100 mg/day). After implantation of the stents, all patients were prescribed ticlopidine (200 mg/day) or clopidogrel (75 mg/day) for at least 1 month post BMS and 12 months post DES. The study was approved by the Ethics Committee of Kobe University and written informed consent for the follow-up OCT study and for inclusion in this study was given by each patient.

### Methods

#### Study Population

This retrospective observational study included patients with ISR associated with the Cypher SES (Cypher, Cordis, Miami Lakes, FL, USA), TAXUS ExpressTM PES (Boston Scientific, Natick, MA, USA), TAXUS LibertéTM PES (Boston Scientific), and BMS between August 2005 and February 2011, who fulfilled the inclusion and exclusion criteria. The inclusion criterion for the study was angiographically documented restenosis (≥50% diameter stenosis) with a DES (SES and PES) or BMS that necessitated referral for target lesion revascularization (TLR) with monitoring by OCT. The exclusion criteria were: (a) left main coronary artery disease, (b) target artery not anatomically suitable for OCT,23 such as an ostial, severely tortuous or heavily calcified lesion, (c) congestive heart failure, (d) renal insufficiency, (e) contraindication for antiplatelet therapy, and (f) a lesion in which a preprocedural OCT examination had not been performed. During this period, OCT was performed if written informed consent was given by the patient.

#### Angiographic Analysis

Coronary angiograms, obtained both at index stent implantation and at the 6–8-month planned follow-up or at the time of re-intervention were analyzed using a computer-based system with edge-detection techniques (Medis Medical Imaging Systems, Leiden, the Netherlands). ISR was defined as ≥50% diameter stenosis of the treated lesion. Based on Mehran’s classification, the angiographic pattern of ISR tissue was classified as focal, diffuse or proliferative. Focal ISR was defined as <10 mm in length and >50% diameter stenosis of the treated lesion. Diffuse ISR was defined as >10 mm in length and >50% diameter stenosis of the treated lesion. Proliferative ISR was defined as >10 mm in length extending beyond either or both margins. For quantitative angiographic analysis, lesion length, reference diameter, minimum lumen area (MLA), and percent stenosis on coronary

---

653

---

![Figure 1. (A) Optical tissue structure of in-stent restenosis: homogeneous (Left), layered (Middle), and heterogeneous (Right), and (B) neointimal tissue area traced for calculation of backscatter, attenuation and mean signal intensity.](image-url)
angiography before stenting were compared between the DES and BMS groups.

**OCT Examination**

OCT examination was performed with coronary artery occlusion as previously reported. Briefly, a 0.016-inch OCT catheter (ImageWire, LightLab Imaging, Westford, MA, USA) was advanced to the distal end of the ISR lesion through an occlusion balloon catheter (Helios®, LightLab Imaging). The occlusion balloon was inflated to 0.5 atm at the proximal site of the ISR lesion, followed by an infusion of lactated Ringer’s solution into the coronary artery from the distal tip of the occlusion balloon catheter at 0.5 ml/s, serving as a flush to clear blood from the area. The entire stented length was then imaged using an automatic pullback system moving at 1 mm/s.

### Quantitative OCT Analysis

Off-line OCT analysis was performed with dedicated software (LightLab Imaging). All images were analyzed by independent observers who were masked to the clinical presentation, lesion characteristics, and stent assignment. For quantitative analysis, cross-sectional OCT images were analyzed at 1-mm intervals. Bifurcation cross-sections with side branches were excluded from the analysis. Sient and lumen areas were manually measured, and NIT area (NITA) was calculated as stent area minus lumen area and NIT thickness was defined as the distance between the stent strut and lumen surface. These were measured for every 1-mm cross-sectional OCT image in the ISR segment.

To evaluate the vascular response after balloon dilatation, ISR lesions treated with balloon angioplasty (BA) were recruited. The response was estimated by the rate of reduction in the NITA, which was defined as NITA before BA minus that after BA divided by NITA before BA in the cross-section of the MLA. The rate of reduction in NITA was compared between stents and among the 3 ISR optical patterns.

### Qualitative OCT Analysis

In the qualitative OCT assessment, the optical appearance of NIT was classified into 3 patterns based on Gonzalo’s classification: homogeneous, layered, and heterogeneous patterns (Figure 1). The homogeneous pattern was characterized by a uniformly signal-rich appearance, containing a mostly signal-rich structure. The layered pattern had a signal-poor appearance with a high-signal band adjacent to the luminal surface. The heterogeneous pattern was mainly signal-poor with islands of various signal regions. There were some cases of mixed optical patterns of NIT and these were classified into one of the 3 morphologic patterns based on the predominant OCT pattern. Two observers judged the OCT findings of the NIT and one of the observers repeated the analysis 1 month later. In addition, lumen shape (regular or irregular) and presence of intraluminal material (protruding mass on the luminal surface of the neointima in the ISR lesion was intraluminal material regardless of the size and extent of signal attenuation) in the ISR lesion were assessed and compared between stents and among OCT patterns.

### Quantifying the Optical Properties of the NIT

Quantification of the optical properties of the NIT was performed using the LightLab software, which has been validated for its efficacy in the quantification of backscatter and attenuation coefficients in the discrimination of atherosclerosis plaques by comparing the results with histology and the diagnostic accuracy of optical intensity in differentiating neointima and fibrin of stent strut coverage. In the present study, whether the quantitative measurement of backscatter, attenuation, and mean signal intensity was useful for identifying the different patterns of NIT in the ISR lesion was addressed by comparing these values among the 3 OCT morphologic patterns. The NITA was manually traced as the lesion of interest on every 1-mm cross-sectional image in the ISR segments (Figure 1) and the software then automatically computed mean signal intensity, attenuation and backscatter of each cross-section.

### Independent Predictor of the Morphologic Patterns and Optical Properties of ISR

In order to estimate the major determinant or variable defining the 3 OCT patterns of homogeneous, layered or heterogeneous NIT and the optical properties of backscatter, attenuation and mean signal intensity, a multivariate analysis was conducted with a set of independent variables from among the baseline variables that were significant in the univariate analysis. In the multivariate analysis of the optical properties, the continuous variables of backscatter, attenuation and mean signal intensity

---

**Table 1. Baseline Characteristics of Patients With a Stent Requiring TLR**

<table>
<thead>
<tr>
<th></th>
<th>DES group (61 patients)</th>
<th>BMS group (38 patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.5±8.12</td>
<td>65.8±10.2</td>
<td>0.17</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48 (79)</td>
<td>32 (84)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (82)</td>
<td>32 (84)</td>
<td>0.77</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>39 (64)</td>
<td>29 (76)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>36 (59)</td>
<td>15 (39)</td>
<td>0.06</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>29 (48)</td>
<td>16 (42)</td>
<td>0.60</td>
</tr>
<tr>
<td>Initial disease</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable AP (%)</td>
<td>31 (51)</td>
<td>9 (24)</td>
<td></td>
</tr>
<tr>
<td>Old MI (%)</td>
<td>12 (19)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ACS (%)</td>
<td>18 (30)</td>
<td>29 (76)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or n (%).

ACS, acute coronary syndrome; AP, angina pectoris; BMS, bare-metal stent; DES, drug-eluting stent; MI, myocardial infarction; TLR, target lesion revascularization.
were dichotomous by their median values as dependent variables.

**Statistical Analysis**

Statistical analysis was performed using StatView 5.0 (SAS Institute, Cary, NC, USA) and SPSS version 16 (SPSS Inc, Chicago, IL, USA). Qualitative data are presented as frequencies and quantitative data are shown as mean values±SD. Categorical variables were compared using χ² or Fisher’s exact test. For continuous variables, comparisons between 2 groups were performed using a 2-tailed, unpaired t-test in equal variances or the Welch t-test in unequal variances. A 2-tailed P-value <0.05 was considered statistically significant. Comparing continuous variables among 3 groups, analysis of variance (ANOVA) was used and the Tukey-Kramer test was performed as post-hoc analysis when there was a significant difference by ANOVA.

To estimate inter- and intraobserver variability of the OCT appearance of NIT, we performed a kappa (κ) test.

**Results**

**Clinical Characteristics**

Baseline patient characteristics are shown in Table 1. All patients continued to take aspirin throughout the follow-up period. Because the subjects of this study were non-randomly selected, patients in the DES group had a lower incidence of acute coronary syndrome with a significantly longer elapsed time than those in the BMS group. Otherwise, there were no significant differences between groups.

**Angiographic Analysis**

Angiographic characteristics at the index stenting procedure and follow-up are shown in Table 2. Reference vessel diameter and percent diameter stenosis were significantly smaller in the DES group than in the BMS group. The angiographic ISR pattern was significantly different between the DES and BMS groups (P<0.01). Diffuse or proliferative ISR was more frequently observed in BMS restenosis than in DES restenosis, whereas focal restenosis was more frequently observed in DES restenosis.

**Qualitative OCT Analysis and Quantification of Optical Properties**

Among the total of 122 lesions examined in this study, 42% were classified as homogeneous, 40% as having a layered pattern, and 18% as heterogeneous. According to the quantitative analysis of the optical properties of the NIT, backscatter was significantly higher in homogeneous and layered ISR tissues than in heterogeneous tissue, and the layered tissue pattern had a significantly higher attenuation than the other 2 types. In terms of the mean signal intensity, the homogeneous pattern had a significantly higher coefficient than the heterogeneous and layered patterns (backscatter: homogenous 7.06±0.41 mm⁻¹ vs. layered 7.06±0.48 mm⁻¹ vs. heterogeneous 6.77±0.28 mm⁻¹; P<0.05, Attenuation: homogenous 1.29±0.76 mm⁻¹ vs. layered 2.24±0.64 mm⁻¹ vs. heterogeneous 1.51±0.71 mm⁻¹; P<0.01, Mean signal intensity: homogenous 6.55±0.30 vs. layered 6.11±0.52 vs. heterogeneous 6.11±0.19; P<0.01).

There was significant difference in the optical morphology of ISR between DES and BMS. The predominant pattern of BMS ISR was homogeneous (n=33, 77.0%), whereas layered (n=42, 53.2%) was frequently observed in DES ISR (Figure 2).

Based on the quantitative analysis of the optical properties of NIT, BMS restenosis tissue had significantly higher backscat-
pendent predictors of the homogeneous pattern (DM: odds ratio (OR) 0.26, confidence interval (CI) 0.10–0.68, P<0.01; DES: OR 0.14, CI 0.046–0.40, P<0.001; MLA: OR 2.26, CI 1.10–4.66, P<0.05), DM, DES and irregular lumen shape for the layered pattern (DM: OR 2.52, CI 1.05–6.01, P<0.05; DES: OR 3.92, CI 1.31–11.8, P<0.05; irregular lumen shape: OR 3.35, CI 1.27–8.82, P<0.05) and none for the heterogeneous pattern. With regard to the optical properties, smoking and DES were independent predictors for backscatter (smoking: OR 0.27, CI 0.11–0.68, P<0.01; DES: OR 0.33, CI 0.13–0.85, P<0.05) and none for mean signal intensity or attenuation.

**Table 3. Optical Characteristics of the ISR Segment**

<table>
<thead>
<tr>
<th></th>
<th>DES group (79 lesions)</th>
<th>BMS group (43 lesions)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCT qualitative assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular lumen shape (%)</td>
<td>20 (25)</td>
<td>8 (19)</td>
<td>0.40</td>
</tr>
<tr>
<td>Intraluminal material (%)</td>
<td>26 (33)</td>
<td>19 (44)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>OCT quantitative assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLA (mm²)</td>
<td>1.49±0.64</td>
<td>1.69±0.91</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean lumen area (mm²)</td>
<td>1.60±0.61</td>
<td>1.82±0.86</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean stent area (mm²)</td>
<td>6.65±1.76</td>
<td>8.23±2.71</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean NITA (mm²)</td>
<td>5.06±1.63</td>
<td>6.41±2.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean percent area stenosis (%)</td>
<td>75.2±8.42</td>
<td>76.8±9.52</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean NIT thickness (mm)</td>
<td>0.74±0.18</td>
<td>0.84±0.51</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>OCT tissue characterization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Backscatter (mm⁻¹)</td>
<td>6.92±0.42</td>
<td>7.14±0.41</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Attenuation (mm⁻¹)</td>
<td>1.69±0.84</td>
<td>1.74±0.81</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean signal intensity</td>
<td>6.20±0.31</td>
<td>6.45±0.39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or n (%). MLA, minimum lumen area; NITA, neointimal tissue area; OCT, optical coherence tomography. Other abbreviations as in Tables 1,2.

**Figure 3.** Difference in optical patterns between in-stent restenosis developing in less and in more than 12 months with drug-eluting stents (Left) and between sirolimus-eluting and paclitaxel-eluting stents (SES/PES) (Right).

The independent variables used in the multivariate analysis were the type of stent (DES or BMS) and the items listed in Tables 1–3. Among 22 baseline variables evaluated, diabetes mellitus (DM), DES and MLA in the ISR lesion were independent predictors of the homogeneous pattern (DM: odds ratio (OR) 0.26, confidence interval (CI) 0.10–0.68, P<0.01; DES: OR 0.14, CI 0.046–0.40, P<0.001; MLA: OR 2.26, CI 1.10–4.66, P<0.05), DM, DES and irregular lumen shape for the layered pattern (DM: OR 2.52, CI 1.05–6.01, P<0.05; DES: OR 3.92, CI 1.31–11.8, P<0.05; irregular lumen shape: OR 3.35, CI 1.27–8.82, P<0.05) and none for the heterogeneous pattern. With regard to the optical properties, smoking and DES were independent predictors for backscatter (smoking: OR 0.27, CI 0.11–0.68, P<0.01; DES: OR 0.33, CI 0.13–0.85, P<0.05) and none for mean signal intensity or attenuation.

**Difference in OCT Findings Based on Time From Stent Implantation**

Among the 122 lesions, 95 (77.9%) had developed ISR <12
Optical Differences in ISR Between DES and BMS

There were no significant differences in the baseline patient and lesion characteristics between lesions following SES implantation (28 lesions in 25 patients) and those following PES implantation (51 lesions in 36 patients), except for follow-up length. The average time from implantation of the stent to the planned follow-up or ischemia-driven TLR was longer with SES than with PES. Among the morphologic patterns of ISR, heterogeneous tissue was more frequently observed with PES, and homogeneous with SES (Figure 3). In the OCT tissue characterization, backscatter, attenuation and mean signal intensity were not significantly different between the 2 stents (backscatter: SES ISR 6.83±0.45 mm⁻¹ vs. PES ISR 6.95±0.41 mm⁻¹; P=0.30; attenuation: SES ISR 1.65±0.80 mm⁻¹ vs. PES ISR 1.70±0.86 mm⁻¹; P=0.82; mean signal intensity: SES ISR 6.16±0.35 vs. PES ISR 6.21±0.30; P=0.54).

Table 4. Procedure and Optical Characteristics of the ISR Segment Before and After BA

<table>
<thead>
<tr>
<th>Type of balloon</th>
<th>Homogeneous (32 lesions)</th>
<th>Layered (30 lesions)</th>
<th>Heterogeneous (14 lesions)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoring or cutting/conventional (semi- or non-compliant)</td>
<td>16/16</td>
<td>18/12</td>
<td>10/4</td>
<td>0.36</td>
</tr>
<tr>
<td>Balloon/stent ratio</td>
<td>1.04±0.08</td>
<td>1.06±0.08</td>
<td>1.04±0.08</td>
<td>0.47</td>
</tr>
<tr>
<td>Maximum dilation pressure (atm)</td>
<td>11.9±3.6</td>
<td>12.8±4.0</td>
<td>12.7±3.5</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Before BA

| MLA (mm²)                  | 1.47±0.81                | 1.28±0.63            | 1.35±0.45                 | 0.57    |
| Stent area (mm²)           | 7.34±2.68                | 6.92±2.38            | 7.27±1.59                 | 0.78    |
| NITA (mm²)                 | 5.87±2.57                | 5.64±2.29            | 5.92±1.82                 | 0.90    |
| Percent area stenosis (%)  | 78.0±11.3                | 80.5±9.09            | 80.2±7.96                 | 0.59    |

After BA

| MLA (mm²)                  | 4.80±1.59                | 5.08±1.86            | 5.37±1.27                 | 0.54    |
| Stent area (mm²)           | 8.92±3.15                | 8.29±2.60            | 8.47±1.71                 | 0.65    |
| NITA (mm²)                 | 4.12±2.00                | 3.20±1.36            | 3.11±1.09                 | <0.05   |
| Percent area stenosis (%)  | 45.0±9.75                | 40.0±12.4            | 36.5±8.55                 | <0.05   |

Values are presented as mean ± SD or n (%).
BA, balloon angioplasty. Other abbreviations as in Tables 1–3.
Vascular Response of ISR to BA

Among the 122 lesions evaluated in this study, the OCT images of 76 lesions were obtained before and after BA (DES ISR: 48 lesions, BMS ISR: 28 lesions). The balloon types used in the study were conventional (semi- and non-compliant balloons), cutting (Flexitome® Cutting Balloon®, Boston Scientific) or scoring (AngioSculpt®, AngioScore, Inc and Lacrosse NSE, Goodman Co, Ltd). The ISR lesions were classified into the 3 groups according to their morphologic pattern (ie, homogeneous: n=32 lesions, layered: n=30, and heterogeneous: n=14). Before BA, there were no significant difference in lumen area, stent area, NITA and percent area stenosis among the 3 patterns on cross-sections of the MLA (Table 4). The ratio of balloon diameter to stent diameter (balloon/stent ratio) and maximum balloon dilation pressure between DES ISR and BMS ISR (conventional/cutting or scoring balloon: DES 21.27, BMS 11.17; P=0.70; balloon/stent ratio: DES 1.0±0.08 vs. BMS 1.02±0.07; P=0.062; maximum dilation pressure: DES 12.7±3.86 atm, BMS 11.9±3.89 atm; P=0.47) or among the 3 OCT patterns (Table 4). The reduction in NITA based on BA was significantly smaller in lesions with the homogeneous pattern than in those with the layered or heterogeneous pattern (reduction rate: homogeneous 29.5±11.9% vs. layered: 42.2±15.7% vs. heterogeneous: 46.3±12.9%; P<0.01, Figure 4). Also, comparing DES ISR and BMS ISR, the DES group tended to have a greater rate of reduction of NITA than the BMS group (reduction rate: DES ISR 40.0±15.9% vs. BMS ISR 33.5±13.3%; P=0.063, Figure 4), probably reflecting the different morphologic properties of ISR tissue in the 2 different stent groups. The reduction rate was not significantly different between lesions treated with SES (42.7±16.5%) and PES (38.3±15.3%; P=0.35).

Discussion

In the present study, ISR was classified as homogeneous, layered or heterogeneous patterns according to the optical morphology of the lesion. The distribution of the 3 patterns significantly differed between the DES and BMS groups. In the DES group, ISR tissue predominantly had a layered pattern, whereas in the BMS group more than half of the ISR lesions had a homogeneous pattern. This study clarifies the differences in ISR structure between DES and BMS based on in-vivo OCT examination of human cases of restenosis.

OCT Assessment of NIT

Pathologic examination of human specimens indicates that NIT after stent implantation has heterogeneous components, including proteoglycan-rich tissue, organized thrombi, smooth muscle cells, atheromas, inflammatory cells, and fibrinoids, that vary according to the time elapsed after stent deployment and the type of stent implanted.1-3 OCT is a robust tool for evaluating NIT coverage after stent deployment and various OCT appearances are considered meaningful in the clinical setting.13-18 in part because the different tissue types have different optical properties, resulting in the various patterns on OCT images as demonstrated in the present study. Recent human pathologic studies reported possible differences between DES and BMS in the components of NIT, there being a greater incidence of fibrinoid deposition, persistent inflammation, and delayed re-endothelialization with DES.4,7,27 and this delayed healing is present even 2 years after DES implantation. Whether or not the delayed healing phenomenon in DES is linked to restenosis is unknown, but several reports suggest that restenosis in DES differs qualitatively from that in BMS.4,7,27,28 ISR tissue after BMS implantation in both autopsy and directional coronary atherecetomy samples is composed mainly of α-smooth muscle actin-positive smooth muscle cells and rare macrophages, embedded in a loose extracellular matrix with partial endothelial regeneration.3 In contrast, organized thrombi and fibrinoids, markers of delayed healing, are often found in the ISR tissue of DES.5,7,27,28

In terms of optical properties, NIT rich in smooth muscle cells with regeneration of dense collagen fibers has high backscatter to optical waves and shows high optical intensity, whereas NIT rich in proteoglycans, cell matrix, and fibrinoids with a low density of smooth muscle cells has a low intensity because of high absorption and multiple scattering of optical waves or low backscattering from penetrating light.29,30 Indeed, results from the present investigation clearly demonstrated that BMS restenosis tissue had a significantly higher mean signal intensity with lower attenuation than DES restenosis tissue. Based on the results of the present study and previous pathologic evaluations of human ISR tissue,1,8 a homogeneous pattern likely comprises mainly smooth muscle cells with collagen fibers, whereas the chief components of the layered and heterogeneous patterns likely include proteoglycans, cell matrix, fibrinoids, and organized thrombi. On the basis of Nagai et al’s case report comparing the morphologic OCT pattern and histology of ISR tissue retrieved by directional coronary atherecetomy,31 it can be speculated that the layered pattern represents NIT comprising proteoglycan-rich tissue with smooth muscle cells richly distributed on the luminal side, and that the heterogeneous pattern indicates NIT comprising organized thrombus and/or fibrinoids with smooth muscle cells poorly and focally distributed. The proportions of these morphologic OCT patterns with DES differs between ISR within 12 months and that which develops in more than 12 months (Figure 6). Considering the higher proportion of the homogeneous pattern for cases of ISR ≥12 months, some of the NIT with a heterogeneous or layered OCT pattern can progress to the homogeneous OCT pattern over time. A larger scale histology-controlled study is warranted to validate our speculation.

Nakazawa et al32 reported atherosclerotic changes within NIT (ie, neoatherosclerosis) in autopsy samples after BMS and DES implantation. In their report, most of the neoatherosclerotic changes within the BMS occurred after more than 6 years, whereas with DES they were more frequently observed within 2 years of stent implantation. Based on their observations, neoatherosclerosis can be contained in some cases of DES ISR, which will affect the optical appearance of the NIT. Despite the various morphologic features of ISR tissue reportedly detected by OCT,19-21 this finding has been rarely reported in previous DES ultrasound studies.10-12 One possible explanation for this might be that OCT has a higher resolution than IVUS, thus providing greater detail of NIT and enabling detection of the structural differences in ISR between DES and BMS. The unique ability of OCT imaging to detect intracoronary microstructure has been confirmed in several experimental and clinical studies.33 The high resolution of OCT technology might enable detection of very subtle differences between DES and BMS in the process of vascular healing in response to stenting.

Nakazawa et al27 demonstrated different histopathologic findings between SES and PES in autopsy samples from patients with stent thrombosis. In patients with SES, there was greater inflammation involving eosinophils, lymphocytes, and giant cells, whereas excessive para-strut fibrin was associated with PES implants. Van Beusekom et al7 also reported that the incidence and extent of fibrinoids were significantly different
between SES and PES. In the present study, optical classification of NIT morphology in ISR lesions revealed a difference between SES and PES, in which the heterogeneous pattern was more frequently observed with PES, while the homogeneous pattern was more frequent with SES. This result may reflect the histological differences between SES and PES, as Van Beusekom et al demonstrated.

Response to BA in ISR Lesions

Recently, unsatisfactory results of repeated DES use for the treatment of DES ISR have been consistently reported. Because there is currently no effective recommended treatment for such cases, simple balloon dilatation of restenotic tissue could be a major treatment strategy. Therefore, we examined the response to BA of vessels in ISR lesions based on OCT. The rate of reduction in NITA tended to be larger in DES ISR than in BMS ISR. Among the optical patterns, the reduction rate was significantly higher in layered or heterogeneous ISR tissue than in homogeneous ISR lesions, suggesting that layered or heterogeneous ISR tissue responds better to simple balloon dilatation than does homogeneous ISR tissue. Thus, based on previous and present findings, simple balloon dilatation is a possible treatment strategy, especially for ISR lesions with a layered or heterogeneous appearance on OCT images, although long-term follow-up studies are necessary to confirm this speculation.

Study Limitations

First, detailed pathology of the 3 types of ISR tissues (homogeneous, layered, and heterogeneous) remains unclear because of the lack of histologic analysis. Currently, however, there are no OCT criteria that have been validated by histology for ISR lesions with a layered or heterogeneous appearance. Second, this study was based on a retrospective analysis with a limited sample size, allowing for the possibility of selection bias. Third, the baseline patient and lesion characteristics were different, which could potentially affect the results of the study. Fourth, because different, which could potentially affect the results of the study. Therefore, we examined the response to BA of vessels in ISR lesions based on OCT. The rate of reduction in NITA tended to be larger in DES ISR than in BMS ISR. Among the optical patterns, the reduction rate was significantly higher in layered or heterogeneous ISR tissue than in homogeneous ISR lesions, suggesting that layered or heterogeneous ISR tissue responds better to simple balloon dilatation than does homogeneous ISR tissue. Thus, based on previous and present findings, simple balloon dilatation is a possible treatment strategy, especially for ISR lesions with a layered or heterogeneous appearance on OCT images, although long-term follow-up studies are necessary to confirm this speculation.

Conclusions

The optical appearance of NIT in ISR lesions was significantly different between SES and BMS, which might reflect their pathologic differences. Optical morphology also differed between SES and PES, with the heterogeneous pattern being more frequently observed with PES, and the homogeneous pattern with SES. The vascular response to BA in the ISR segments with different OCT morphologic appearances varied significantly. Morphologic OCT evaluation of restenosis tissue may offer important clinical information about the vascular response to BA, suggesting a possible direction for OCT-based ISR treatment strategies.

Disclosures

Conflict of Interest: None declared.

References


